Answer 1:

Bibliographic Information

Synergistic antitumor activity of capecitabine in combination with irinotecan. Cao, Shousong; Durrani, Farukh A.; Rustum, Youcef M. Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Colorectal Cancer (2005), 4(5), 336-343. Publisher: Cancer Information Group, CODEN: CCCLCF ISSN: 1533-0028. Journal written in English. CAN 142:385338 AN 2005:198981 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

5-Fluorouracil (5-FU) and capecitabine alone and in combination with irinotecan/oxaliplatin are clin. active in the treatment of colorectal and other solid tumors. Studies of the antitumor activity and toxicity of capecitabine or irinotecan alone and in combination with each other, were compared with 5-FU and raltitrexed in human tumor xenografts of colorectal and squamous cell carcinoma of the head and neck using clin. relevant schedules. Antitumor activity and toxicity were evaluated in nude mice bearing human colon carcinomas of HCT-8 and HT-29 and in head and neck squamous cell carcinomas of A253 and FaDu xenografts using the max. tolerable dose of single-agent capecitabine, 5-FU, or raltitrexed, or each of the drugs in combination with irinotecan. Mice were treated with capecitabine and irinotecan alone or in combination using 2 different schedules: (1) capecitabine orally once a day for 7 days and a single dose of irinotecan (50 mg/kg i.v.), with each drug alone or in combination, and (2) capecitabine orally 5 days a week for 3 wk and irinotecan 50 mg/kg (I.V. injection) once a week for 3 wk, with each drug alone or in combination. For comparative purposes, the antitumor activity of single-agent capecitabine, 5-FU, or raltitrexed, or each drug in combination with irinotecan was carried out at its max. tolerated dose (MTD) using a 3-wk schedule. Results indicated that HT-29 and A253 xenografts were de novo resistant (no cure) to capecitabine and irinotecan alone at the MTD, whereas HCT-8 and FaDu xenografts were relatively more sensitive, yielding 10-20% cures. The combination of irinotecan/capecitabine was much more active than either drug alone against all 4 tumor models. The cure rates were increased from 0 to 20% in A253 and HT-29 xenografts and from 10-20% to 80-100% in HCT-8 and FaDu tumor xenografts, resp. Irinotecan/capecitabine had clear advantage over irinotecan/5-FU and irinotecan/raltitrexed in efficacy and selectivity in that they were more active and less toxic.

The extent of synergy with irinotecan/capecitabine appears to be tumor-dependent and independent of the status of p53 expression. The potential impact of the preclin. results on clin. practice for the use of these drugs in combination needs clin. validation.

Answer 2:

Bibliographic Information

Antifolates targeted specifically to the folate receptor. Jackman, Ann L.; Theti, Davinder S.; Gibbs, David D. Section of Medicine, Institute of Cancer Research, Sutton, Surrey, UK. Advanced Drug Delivery Reviews (2004), 56(8), 1111-1125. Publisher: Elsevier Science B.V., CODEN: ADDREP ISSN: 0169-409X. Journal; General Review written in English. CAN 140:385347 AN 2004:319861 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

A review. Most antifolate drugs are efficiently transported by the reduced-folate carrier (RFC). However, several also bind with high affinity to the α-isoform of the folate receptor (α-FR) and there is evidence to suggest that this transport mechanism may contribute to their activity when the receptor is highly overexpressed or when the extracellular folate concn. is very low. In particular, the presence of the α-FR on tumor cell lines sensitizes them to brief exposures to ZD9331. Nevertheless, it is the ubiquitous expression of the RFC in normal tissues that reduces patient tolerability to antifolate drugs. The overexpression of the α-FR in some epithelial tumors and its restricted distribution in normal tissues suggests an opportunity for the development of antifolates specifically targeted at α-FR overexpressing tumors. Potent cyclopenta[g]quinazoline-based inhibitors of thymidylate synthase (TS) were discovered with high and low affinity for the α-FR and RFC, resp. This class of agent is represented by CB300638 (TS Ki=0.24 nM) that displays high potency (IC50.apprx.3 nM) for A431-FBP cells (transfected with the α-FR) and KB cells (constitutive overexpression). Importantly, this activity is .apprx.300-fold higher than for α-FR neg. cell lines such as A431. In mice bearing the KB tumor xenograft the authors

have demonstrated localization of CB300638 to tumor and, more importantly, specific inhibition of TS in tumor and not in normal tissues. Data supports the clin. development of this class of agent with the prediction that toxicity would be reduced compared with conventional antifolate drugs. There are a no. of challenges to this development posed by the uniqueness of the compds. and these are discussed.

Answer 3:

Bibliographic Information

A potential important role for thymidylate synthetase inhibition on antitumor activity of fluoropyrimidine and raltitrexed. Kabeshima, Yasuo; Kubota, Tetsuro; Watanabe, Masahiko; Saikawa, Yoshiro; Nishibori, Hideki; Hasegawa, Hirotoshi; Kitajima, Masaki. Department of Surgery, School of Medicine, Keio University, Tokyo, Japan. Anticancer Research (2002), 22(6A), 3245-3252. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 139:190772 AN 2003:87838 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Because thymidylate synthetase (TS) is a key enzyme in DNA synthesis, it has been used as a target for cancer chemotherapy. We investigated the combined antitumor activity of raltitrexed, 5-FU and UFT on human tumor xenografts in nude mice and examd. changes in TS activity and 5-FU-bound RNA (F-RNA) levels. Human gastric (SC-1-NU) or colon (HT-29) carcinoma xenografts were transplanted s.c. into nude mice, and drugs administered i.p. (raltitrexed and 5-FU) or perorally (UFT) daily for 5 days, and repeated once after a 2-day interval. The antitumor effects were mostly equiv. between the treatment groups despite the different drugs and sequence orders. TS inhibition rates correlated with the tumor inhibition rate, which was statistically significant, while F-RNA levels did not correlate with antitumor activity. Our results indicated that the combination of fluoropyrimidine-related agents should be directed towards increased TS inhibition rather than increased F-RNA levels.

Answer 4:

Bibliographic Information

Synergistic efficacy of 3n-Butyrate and 5-fluorouracil in human colorectal cancer xenografts via modulation of DNA synthesis. Bras-Goncalves, Rui Alberto; Pocard, Marc; Formento, Jean-Louis; Poirson-Bichat, Florence; De Pinieux, Gonzague; Pandrea, Ivona; Arvelo, Francisco; Ronco, Gino; Villa, Pierre; Coquelle, Arnaud; Milano, Gerard; Lesuffleur, Thecla; Dutrillaux, Bernard; Poupon, Marie-France. Laboratoire de Cytogenetique Moleculaire et Oncologie, UMR 147 CNRS-Institut Curie, Paris, Fr. Gastroenterology (2001), 120(4), 874-888. Publisher: W. B. Saunders Co., CODEN: GASTAB ISSN: 0016-5085. Journal written in English. CAN 135:174845 AN 2001:233856 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Background & Aims: Butyrate, produced in the colon lumen, maintains mucosal cell homeostasis. Poorly diffusible, its access is compromised in growing colon cancers and absent in distant metastases. Butyrate regulates DNA synthesis. We postulated that systemic administration of butyrate should reduce colon cancer growth and enhance 5-fluorouracil (5-FU) efficacy. Methods: A stable deriv. of butyrate (3n-But) was used. The antitumoral efficacy of 5-FU and 3n-But, alone or combined, was evaluated in human colorectal cancers (hCRCs) s.c., orthotopically, or intrasplenically grafted into nude mice. Thymidylate synthase (TS) and thymidine kinase (TK) mRNA expression, proliferation, apoptosis, and cell cycle alterations were studied. Results: In vivo, 5-FU alone inhibited growth of only 3 of the 12 hCRCs tested and 3n-But alone had no effect; the 5-FU/3n-But combination inhibited growth of all 16 hCRCs tested. The hCRCs differed in their p53 and microsatellite instability status. 5-FU/3n-But decreased TK and TS mRNA expression by 20- and 40-fold, resp., and TS activity by 75%, stopped cell proliferation without affecting cell differentiation, and significantly enhanced apoptosis. 3N-But potentiated the efficacy of Tomudex and methotrexate, 2 TS inhibitors, but not that of oxaliplatin. In vitro, 5-FU/3n-But inhibited [3H]thymidine but not bromodeoxyuridine incorporation and induced apoptosis in hCRC cell lines. Cells treated with 5-FU/3n-But did not accumulate in G1 nor in S phase of the cell cycle, while 5-FU and 3n-But arrested the cycle in S and in G1 phase, resp. 3N-But prevented the cell rescue from 5-FU-induced cytotoxicity by uridine or thymidine.

Conclusions: 3n-But and TS inhibitors acted synergistically against colorectal cancers, independently of the genetic alterations of the hCRCs. The mechanism of action of 5-FU/3n-But could be enhanced redn. of TS and prevention of thymidine salvage in DNA synthesis.

Answer 5:

Bibliographic Information

Quantification of tumor cell injury in vitro and in vivo using expression of green fluorescent protein under the control of the GADD153 promoter. Lin, Xinjian; Gately, Dennis P.; Hom, Doreen; Mishima, Misako; Los, Gerrit; Howell, Stephen B. Department of Medicine and the Cancer Center, University of California at San Diego, La Jolla, CA, USA. International Journal of Cancer (2001), 91(4), 555-562. Publisher: Wiley-Liss, Inc., CODEN: IJCNAW ISSN: 0020-7136. Journal written in English. CAN 135:162045 AN 2001:128247 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The GADD153 gene is strongly transcriptionally activated by many types of cellular injury and the magnitude of the change in GADD153 expression is proportional to the extent of damage. We developed a novel reporter system in which a chimeric gene contg. the GADD153 promoter linked to the coding region of an enhanced green fluorescent protein (EGFP) gene was stably integrated into the genome of a clone of UMSCC10b head and neck carcinoma cells. Activation of the exogenous GADD153 promoter was quantified using flow cytometric measurement of EGFP expression following drug exposure. The exogenous GADD153 promoter in this clone was activated by N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) in a concn.-dependent manner with kinetics that closely paralleled perturbation of cell cycle phase distribution. EGFP expression was strongly activated by a variety of genotoxic agents including DNA crosslinking and methylating agents, oxygen free radicals, DNA intercalator, UV and γ-radiation and hypoxia. When grown as a xenograft in nude mice, the stably transfected clone also demonstrated dose-dependent EGFP expression when measured 4 days after cisplatin treatment. The reporter system accurately categorized the relative potency of adducts produced by 6 related platinum-contg. drugs. In conclusion, this reporter system can facilitate in vitro and in vivo screening for agents capable of producing cytotoxicity via a wide variety of different mechanisms, and can be utilized to investigate the relative potency of structurally related DNA adducts.

Answer 6:

Bibliographic Information

Antitumor effect and potentiation of cytotoxic drugs activity in human cancer cells by ZD-1839 (Iressa), an epidermal growth factor receptor-selective tyrosine kinase inhibitor. Ciardiello, Fortunato; Caputo, Rosa; Bianco, Roberto; Damiano, Vincenzo; Pomatico, Grazia; De Placido, Sabino; Bianco, A. Raffaele; Tortora, Giampaolo. Cattedra di Oncologia Medica, Universita degli Studi di Napoli Federico II, Naples, Italy. Clinical Cancer Research (2000), 6(5), 2053-2063. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 133:275993 AN 2000:401145 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Transforming growth factor α (TGF-α) is an autocrine growth factor for human cancer. Overexpression of TGF-α and its specific receptor, the epidermal growth factor receptor (EGFR), is assocd. with aggressive disease and poor prognosis. The EGFR has been proposed as a target for anticancer therapy. Compds. that block ligand-induced EGFR activation have been developed. ZD-1839 (Iressa) is a p.o.-active, quinazoline deriv. that selectively inhibits the EGFR tyrosine kinase and is under clin. development in cancer patients. The antiproliferative activity of ZD-1839 alone or in combination with cytotoxic drugs differing in mechanism(s) of action, such as cisplatin, carboplatin, oxaliplatin, paclitaxel, docetaxel, doxorubicin, etoposide, topotecan, and raltitrexed, was evaluated in human ovarian (OVCAR-3), breast (ZR-75-1, MCF-10A ras), and colon cancer (GEO) cells that coexpress EGFR and TGF-α. ZD-1839 inhibited colony formation in soft agar in a dose-dependent manner in all cancer cell lines. The antiproliferative effect was mainly cytostatic. However, treatment with higher doses resulted in a 2-4-fold increase in apoptosis. A dose-dependent supra-additive

increase in growth inhibition was obsd. when cancer cells were treated with each cytotoxic drug and ZD-1839. The combined treatment markedly enhanced apoptotic cell death induced by single-agent treatment. ZD-1839 treatment of nude mice bearing established human GEO colon cancer xenografts revealed a reversible dose-dependent inhibition of tumor growth because GEO tumors resumed the growth rate of controls at the end of the treatment. In contrast, the combined treatment with a cytotoxic agent, such as topotecan, raltitrexed, or paclitaxel, and ZD-1839 produced tumor growth arrest in all mice. Tumors grew slowly for approx. 4-8 wk after the end of treatment, when they finally resumed a growth rate similar to controls.

GEO tumors reached a size not compatible with normal life in all control mice within 4-6 wk and in all single agent-treated mice within 6-8 wk after GEO cell injection. In contrast, 50% of mice treated with ZD-1839 plus topotecan, raltitrexed, or paclitaxel were still alive 10, 12, and 15 wk after cancer cell injection, resp. These results demonstrate the antitumor effect of this EGFR-selective tyrosine kinase inhibitor and provide a rationale for its clin. evaluation in combination with cytotoxic drugs.

Answer 7:

Bibliographic Information

Overexpression of Bax enhances antitumor activity of chemotherapeutic agents in human head and neck squamous cell carcinoma. Guo, Bin; Cao, Shousong; Toth, Karoly; Azrak, Rami G.; Rustum, Youcef M. Department of Pharmacology and Experimental Therapeutics, Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Cancer Research (2000), 6(2), 718-724. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 133:53286 AN 2000:162761 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

Overexpression of the Bax protein in human head and neck squamous cell carcinoma A253 cells was reported to result in an increased sensitivity to various chemotherapeutic agents in vitro. In the present study, the relationship between Bax expression and response to chemotherapy was further investigated in vitro in vivo model systems. For in vitro study, A253, A253/Vec (pcDNA3 vector transfectant), and A253/Bax (pcDNA3/Bax transfectant, expressing 50-fold higher Bax protein than A253 and A253/Vec) cells were exposed to various concns. of raltitrexed (a specific thymidylate synthase inhibitor) and SN-38 (a topoisomerase I inhibitor) for 2 h, and cell growth inhibition was assessed by 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide clonogenic assay. Compared to A253/Vec, A253/Bax cells exhibited 9.5- and 13.8-fold increases in sensitivity to raltitrexed and SN-38, resp. For in vivo study, A253/Vec and A253/Bax tumor xenografts were established by s.c. injection of tumor cells into nude mice. The antitumor activity and toxicity of raltitrexed (i.v. push daily for 5 days) and irinotecan (a prodrug of SN-38; i.v. push daily for 3 days) were evaluated. The max. tolerated doses of raltitrexed and irinotecan were 30 and 100 mg/kg/day, resp. At the max. tolerated doses, minimal antitumor activity was obsd. with raltitrexed, although irinotecan was more active than raltitrexed against A253 or A253/Vec tumors. In contrast, both raltitrexed and irinotecan were more active against A253/Bax xenografts than against A253/Vec xenografts; the yield for complete tumor regression (cure) was 40% and 100% with raltitrexed and irinotecan, resp., with no significant toxicity. Furthermore, the obsd. increase of antitumor activity in A253/Bax tumors was assocd. with an enhanced induction of apoptosis in vivo.

The in vivo results demonstrated a proof of the principal concept that selecting up-regulation of the proapoptosis gene Bax can provide the basis for a greater therapeutic efficacy to a variety of chemotherapeutic agents with different structures and mechanisms of action.

Answer 8:

Bibliographic Information

Antitumor activity of ZD1694 (tomudex) against human head and neck cancer in nude mouse models: role of dosing schedule and plasma thymidine. Cao, Shousong; McGuire, John J.; Rustum, Youcef M. Grace Cancer Drug Center, Roswell Park Cancer Institute, Buffalo, NY, USA. Clinical Cancer Research (1999), 5(7), 1925-1934. Publisher: American Association for Cancer Research, CODEN: CCREF4 ISSN: 1078-0432. Journal written in English. CAN 131:237626 AN 1999:504960 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

We studied the antitumor activity and toxicity of ZD1694 (tomudex), a specific inhibitor of thymidylate synthase (TS), in nude mice bearing human head and neck squamous cell carcinoma A253 and FaDu xenografts. Mice were treated by single i.v. push (i.v. × 1), i.v. push once a week for 3 wk (weekly × 3), and i.v. push once a day for 5 days (daily × 5), and the max. tolerated doses (MTDs) of ZD1694 were 300 mg/kg, 60 mg/kg/wk, and 30 mg/kg/day, resp. ZD1694 was moderately active against both A253 and FaDu xenografts. Antitumor activity was schedule-dependent in both tumors: weekly × 3 ≥ i.v. × 1 .mchgt. daily × 5. In contrast, the rank order of toxicity was daily × 5 .mchgt. weekly × 3 ≥ i.v. × 1. ZD1694 at the MTD produced 20% complete tumor regression and 20% partial tumor regression (PR) with i.v. × 1 and weekly × 3 schedules and 12-day tumor growth delay with daily × 5 schedule against FaDu xenografts. No complete tumor regression was achieved with ZD1694 with any schedule against A253; a 20% PR, 40% PR, and 10-day tumor growth delay were obsd. with i.v. × 1, weekly × 3, and daily × 5 schedules, resp. The data indicate that ZD1694 was slightly more effective against FaDu than against A253. Of interest and potential clin. importance was the observation that ZD1694 was still active at doses lower than the MTD (≥1/3 MTD), which showed a high therapeutic index and wide safety margin. Study of ZD1694 compared with 5-fluorouracil and 5-fluoro-2'-deoxyuridine at the MTD revealed that the antitumor activity of ZD1694 was comparable with or superior to 5-fluorouracil and 5-fluoro-2'-deoxyuridine against both A253 and FaDu xenografts, with less toxicity. High plasma thymidine in mouse relative to human (≈1.3 μM and <0.1 μM, resp.) may complicate the study of antitumor activity and toxicity of TS inhibitors with human tumor xenografts grown in the mouse. To test this hypothesis, we preadministered methoxypolyethyleneglycol-conjugated thymidine phosphorylase (MPEG-TPase;

2500 units/kg/dose) to reduce mouse plasma thymidine, then treated with various doses of ZD1694 using the daily × 5 or i.v. × 1 schedules in the A253 tumor model. MPEG-TPase significantly increased the toxicity of ZD1694; the MTD of ZD1694 plus MPEG-TPase was reduced 3- and 10-fold compared with ZD1694 alone for i.v × 1 and daily × 5 schedules, resp. However, preadministration of MPEG-TPase did not potentiate the antitumor activity of ZD1694 with either schedule. The data indicate that the study of TS inhibitors in rodent models may not be suitable for predicting a safe dose for clin. study. However, rodent models, particularly human tumor xenografts, are still useful models for evaluation of antitumor activity and schedule selection for TS inhibitors.

Answer 9:

Bibliographic Information

Role of thymidylate synthase in the antitumor activity of the multitargeted antifolate, LY231514. Schultz, Richard M.; Patel, Vinod F.; Worzalla, John F.; Shih, Chuan. Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, IN, USA. Anticancer Research (1999), 19(1A), 437-443. Publisher: International Institute of Anticancer Research, CODEN: ANTRD4 ISSN: 0250-7005. Journal written in English. CAN 131:111018 AN 1999:298094 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The cytotoxicity of LY231514 was only partially alleviated by thymidine addn. (5 μM) in GC3 human colon carcinoma cells, and complete protection required the addn. of both hypoxanthine (100 μM) and thymidine. In contrast, the cytotoxic activity of tomudex (raltitrexed, ZD1694) was completely reversed by thymidine alone. MCF-7 human breast and H630 human colon carcinoma cells selected for resistance to tomudex and 5-fluorouracil, resp. via thymidylate synthase (TS) amplification demonstrated only modest resistance to LY231514 compared to tomudex. LY231514-induced cytotoxicity in these resistant cell lines was completely prevented by the addn. of hypoxanthine (100 μM), indicating inhibition of purine de novo biosynthesis as a secondary target for LY231514 action. Thymidine at physiol. levels in mouse plasma (approx. 1 μM) produced only a 2.6-fold shift in the IC50 for LY231514-mediated cytotoxicity in GC3/cl1 cells compared to a 128-fold shift for tomudex. LY231514 treatment (i.p., qd ×10) significantly delayed tumor growth in the GC3 carcinoma xenograft model. However, a thymidine kinase-deficient mutant of this same tumor line demonstrated heightened sensitivity to the in vivo antitumor activity of LY231514 with complete regression of established tumors and a large no. of tumor-free survivors after one course of treatment. The data demonstrate that inhibition of thymidylate synthase is a prominent mechanism for antitumor activity by LY231514, but important secondary sites of action exist for this multitargeted mol.

Answer 10:

Bibliographic Information

Interaction of Tomudex with radiation in vitro and in vivo. Teicher, Beverly A.; Ara, Gulshan; Chen, Ying-Nan; Recht, Abram;

Coleman, C. Norman. Dana-Farber Cancer Institute and Joint Center for Radiation Therapy, Boston, MA, USA. International Journal of Oncology (1998), 13(3), 437-442. Publisher: International Journal of Oncology, CODEN: IJONES ISSN: 1019-6439. Journal written in English. CAN 129:312898 AN 1998:566560 CAPLUS (Copyright (C) 2008 ACS on SciFinder (R))

Abstract

The potential of the thymidylate synthase inhibitor, Tomudex to interact with ionizing radiation was assessed in vitro and in vivo in comparison with 5-fluorouracil. A concn. of 1 μM Tomudex decreased the shoulder of the radiation survival curves for normally oxygenated and hypoxic human HT-29 colon carcinoma cells and human SCC-25 head and neck squamous carcinoma cells, resulting in enhancement ratios of 10 and 2.8 for normally oxygenated and hypoxic HT-29 cells at 5 Gy, resp., and enhancement ratios of 19.5 and 2.7 for normally oxygenated and hypoxic SCC-25 cell at 5 Gy, resp. Two schedules of Tomudex administered to animals bearing the Lewis lung carcinoma resulted in additive tumor growth delay with the fractionated radiation therapy. In nude mice bearing the HT-29 colon carcinoma grown as a xenograft, administration of Tomudex daily for 5 days on a 1 or 2-wk schedule resulted in increased tumor growth delay along with fractionated radiation therapy on the same schedules. However, administration of Tomudex intermittently on a 2-wk schedule appeared to be more interactive with daily fractionated radiation therapy on the 2-wk schedule. In each assay, the results obtained with Tomudex were equal to or exceeded those obtained with 5-fluorouracil. These findings indicate that clin. trial of Tomudex along with fractionated radiation therapy is warranted.

Answer 11:

Bibliographic Information

A preclinical evaluation of pemetrexed and irinotecan combination as second-line chemotherapy in pancreatic cancer. Mercalli A; Sordi V; Formicola R; Dandrea M; Beghelli S; Scarpa A; Di Carlo V; Reni M; Piemonti L Laboratory of Experimental Surgery, San Raffaele Scientific Institute, Via Olgettina 60, Milan 20132, Italy British journal of cancer (2007), 96(9), 1358-67. Journal code: 0370635. ISSN:0007-0920. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 17426706 AN 2007262882 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

Gemcitabine (GEM)-based chemotherapy is regarded as the standard treatment of pancreatic adenocarcinoma, but yields a very limited disease control. Very few studies have investigated salvage chemotherapy after failure of GEM or GEM-containing chemotherapy and preclinical studies attempting to widen the therapeutic armamentarium, not including GEM, are warranted. MIA PaCa2, CFPAC-1 and Capan-1 pancreatic cancer cell lines were treated with GEM, fluouracil (5-FU), docetaxel (DCT), oxaliplatin (OXP), irinotecan (CPT-11), pemetrexed (PMX) and raltitrexed (RTX) as single agent. Pemetrexed, inducing apoptosis with IC50s under the Cmax in the three lines tested, appeared the most effective drug as single agent. Based on these results, schedule- and concentration-dependent drug interactions (assessed using the combination index) of PMX/GEM, PMX/DCT and PMX-CPT-11 were evaluated. The combinatory study clearly indicated the PMX and CPT-11 combination as the most active against pancreatic cancer. To confirm the efficacy of PMX-CPT-11 combination, we extended the study to a panel of 10 pancreatic cancer cell lines using clinically relevant concentrations (PMX 10 microM; CPT-11 1 microm). In eight of 10 lines, the PMX-CPT-11 treatment significantly reduced cell recovery and increased both the subG1 and caspase 3/7 fraction. After a 5-day wash out period, an increased fraction of subG1 and caspase3/7 persisted in PMX-CPT-11-pretreated cell lines and a significant reduction in the clonogenicity capacity was evident. Finally, in vivo, the PMX/CPT-11 combination showed the ability to inhibit xenograft tumours growth as second-line therapy after GEM treatment. The PMX and CPT-11 combination displays a strong schedule-independent synergistic cytotoxic activity against pancreatic cancer, providing experimental basis for its clinical testing as salvage chemotherapy in pancreatic cancer patients.

Answer 12:

Bibliographic Information

An evaluation of thymidine phosphorylase as a means of preventing thymidine rescue from the thymidylate synthase inhibitor raltitrexed. Graham-Cole Claire L; Thomas Huw D; Taylor Gordon A; Newell David R; Melton Roger G; Hesp Richard; Boddy Alan V Northern Institute for Cancer Research, Medical School, University of Newcastle, Newcastle upon Tyne, NE2 4HH, UK Cancer chemotherapy and pharmacology (2007), 59(2), 197-206. Journal code: 7806519. ISSN:0344-5704. Journal; Article; (JOURNAL ARTICLE) written in English. PubMed ID 16721548 AN 2006697078 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

The antitumour effect of thymidylate synthase inhibitors such as raltitrexed (RTX) may be reversed by salvage of thymidine (Thd). Since thymidine phosphorylase (TP) depletes Thd, the potential for tumour-selective depletion of Thd using antibody-mediated delivery of TP to tumours was investigated. In vitro studies demonstrated that 25 x 10(-3) units/ml TP depleted extracellular Thd (3 microM) and restored sensitivity to the growth inhibitory effects of RTX in Lovo and HT29 cell lines. Thymidine concentrations in xenograft tumours were inversely proportional to the activity of TP in the tumour, and the presence of a subcutaneous Lovo xenograft reduced plasma Thd concentrations from 0.92 +/- 0.07 to 0.37 +/- 0.04 microM. Intravenous administration of native TP enzyme depleted plasma Thd to 5 nM, but following rapid elimination of TP, plasma Thd returned to pretreatment values. There was no effect on tumour TP or Thd. Conjugation of TP to the A5B7 F(ab)2 antibody fragment, which targets carcinoembryonic antigen (CEA) expressed on colorectal cell-lines such as Lovo, did result in selective accumulation of TP in the tumour. However, there was no tumour-selective depletion of Thd and there did not appear to be any potential benefit of combining antibody-targeted TP with RTX.

Answer 13:

Bibliographic Information

Up-regulation in dihydropyrimidine dehydrogenase activity by raltitrexed causes antagonism in combination with 5-fluorouracil. Nozoe Yasuhiro; Ogata Yutaka; Araki Yasumi; Sasatomi Teruo; Fukumori Hiroyuki; Shirouzu Kazuo Department of Surgery, Kurume University School of Medicine, 67-Asahi-machi, Kurume-City, Fukuoka, 831-0011, Japan Anticancer research (2003), 23(6C), 4663-9. Journal code: 8102988. ISSN:0250-7005. Journal; Article; (JOURNAL ARTICLE); (RESEARCH SUPPORT, NON-U.S. GOV'T) written in English. PubMed ID 14981911 AN 2004092822 MEDLINE (Copyright (C) 2008 U.S. National Library of Medicine on SciFinder (R))

Abstract

BACKGROUND AND METHODS: We have studied the influence of raltitrexed, a specific thymidylate synthase (TS) inhibitor, on dihydropyrimidine dehydrogenase (DPD) activity in cultured cancer cells and in transplanted tumors in nude mice. Further, we investigated the combined effect of raltirexed and 5-fluorouracil (5-FU) on the in vitro anti-tumor effect and its correlation to the DPD activity and mRNA level. RESULTS: By raltitrexed treatment, the DPD activity and mRNA level were increased in HuTu-80 small intestine carcinoma cells, and in its transplanted tumors. On the other hand, raltitrexed showed no influence on DPD activity in MIAPaCa2 pancreatic carcinoma cells. In the study of cell growth activity, the results showed that in MIAPaCa2, the Combination Index (CI) was 0.57 +/- 0.03, representing a synergistic effect, while in HuTu-80, the CI was 1.26 +/- 0.09, representing an antagonistic effect. CONCLUSION: Raltitrexed may up-regulate DPD activity in tumor cells, resulting in antagonism when combined with 5-FU.

Answer 14:

Bibliographic Information

Characterization and drug sensitivity of four newly established colon adenocarcinoma cell lines to antifolate inhibitors of thymidylate synthase. Longo G S; Izzo J; Gorlick R; Banerjee D; Jhanwar S C; Bertino J R Laboratory of Molecular Pharmacology and Experimental Therapeutics, Memorial Sloan-Kettering Cancer Center, New York, NY 10021, USA Oncology research (2001), 12(8), 309-14. Journal code: 9208097. ISSN:0965-0407.

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Abstract

Four new cell lines were established from the primary tumors of patients with untreated colorectal adenocarcinoma. Drug sensitivity and characterization of these cell lines was performed. Three of the four cell lines formed colonies in soft agar and all were tumorigenic in nude mice. The cell lines were morphologically similar but had differences in growth characteristics. Two of the cell lines, C18 (CCCL-4) and C29 (CCCL-6), had a longer doubling time compared with C85 (CCCL-1) and C86 (CCCL-2). The C18 and C29 cell lines had chromosome 17 abnormalities and evidence by immunohistochemistry of a mutant p53 and had decreased levels of thymidylate synthase and dihydrofolate reductase proteins, associated with decreased thymidylate synthase catalytic activity in C18 and no detectable activity in C29. Raltitrexed and GW1843U89 showed potent cytotoxic activity and all four cell lines displayed similar cytotoxicity to these folate thymidylate synthase inhibitors. The C18 and C29 cell lines were in general resistant to the other agents tested (methotrexate, 5-fluorouracil, nolatrexed) when compared with the C85 and C86 cell lines. These new cell lines may be useful for the study of colorectal adenocarcinoma and for evaluating new drugs or treatment schedules.